POST-OPERATIVE ANALGESIA
A COMPARATIVE STUDY OF INTRATHECAL BUPIVACAINE WITH BUPRENORPHINE AND INTRATHECAL BUPIVACAINE WITH MIDAZOLAM

Dissertation submitted
in partial fulfillment of

PART - II - M.D. (BRANCH - X)

ANAESTHESIOLOGY

THE TAMILNADU DR.MGR MEDICAL UNIVERSITY, CHENNAI.

STANLEY MEDICAL COLLEGE

CHENNAI.

MARCH, 2007

CERTIFICATE

This is to certify that the dissertation work on **POST-OPERATIVE ANALGESIA A COMPARATIVE STUDY OF INTRATHECAL BUPIVACAINE WITH BUPRENORPHINE AND INTRATHECAL BUPIVACAINE WITH MIDAZOLAM** is the bonafide work done by Dr.D.Gopinath, Govt. Stanley Medical College and Hospital, Chennai – 600001 under my supervision and guidance in partial fulfillment of the regulations laid down by The Tamil Nadu Dr. M.G.R.Medical University, for the M.D., Anaesthesiology Branch X course during the academic period of May 2005 to March 2007.

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DECLARATION

I, **Dr D.GOPINATH** solemnly declare that this dissertation titled **POST-OPERATIVE ANALGESIA A COMPARATIVE STUDY OF INTRATHECAL BUPIVACAINE WITH BUPRENORPHINE AND INTRATHECAL BUPIVACAINE WITH MIDAZOLAM** is a bonafide record of work done by me in the Department of Anaesthesiology, Govt. Stanley Medical College and Hospital, Chennai under the guidance of Professor **Dr.R.MEENAKSHI,** M.D., D.A. Departnent of Anaesthesiology, Govt Stanley Medical College, Chennai.

This dissertation is submitted to The TamilNadu Dr. M.G.R. Medical University Chennai, in partial fulfillment of the University regulations for the award of degree of M.D., Branch X (Anaesthesiology) examination to be held in March 2007.

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ACKNOWLEDGEMENT

I gratefully acknowledge and sincerely thank Dr.D.R.Gunasekaran, M.S.,F.I.C.S., Dean, Stanley Medical College, Chennai for granting me permission to utilize the facilities of the institution for my study.

I wish to express my grateful thanks to :

Dr.R.Meenakshi, M.D., D.A., Professor and Head of Department of Anaesthesiology, Govt. Stanley Medical College, Chennai for her valuable advice and constant supervision and encouragement.

Additional Professors, **Dr.C.R.Kanyakumari, M.D.,D.A., Dr.S.Nellai Kumar, M.D., D.A.,** and **Dr. Vasanthi, M.D.,D.A.,** for their valuable suggestions and consistent support.

Additional Professors, **Dr.Esther Sudarshini Rajkumar, M.D.,D.A., Dr.D.Gandhimathi, M.D.,D.A.,** for their help and encouragement.

All Assistant Professors, Department of Anaesthesiology, Stanely Medical College and Hospital, for their help and support.

The Professors and Assistant Professors, Department of Orthopaedics, Stanley Medical College and Hospital for their co-operation.

The patients included in the study and their relatives.

CONTENTS

INTRODUCTION

Pain is one of the commonest and most unpleasant symptom that leads the patient to seek medical advice and whatever may be the cause it demands relief. Pain is a sensation which produces a reaction consisting of withdrawal response ,metabolic response, hormonal response and conscious aversion.

Pain has been defined by IASP [International association for study of pain] as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage .The relief of post-operative pain is a subject which has been receiving an increasing amount of attention in the past few years

Pain relief is necessary for 1.Humanitarian and 2. Therapeutic reasons. Pain relief must be 1.Effective 2.Safe 3.feasible Post operative pain relief is important in reducing the morbidity after surgery .Pain causes peripheral vasoconstriction, reduces functional residual capacity and sputum clearance.

Post operative pain relief has the following advantages-it can reduce the metabolic response to trauma, thus may prevent negative nitrogen balance. Moreover the pain relieved patient has better mobility with reduced incidence of chest infections and deep vein thrombosis. Patients with Hypertension and ischemic heart disease, when allowed to experience pain in the post operative period may develop a reactionary rise in blood pressure,tachycardia and may go for subendocardial ischemia, infarction, hence the need for post operative pain relief [1,2].

Spinal anaesthesia continues to be one of the commonest regional anaesthetic

techniques because of rapid onset, safety and simplicity. The use of neuraxial additive drugs with local anaesthetic agents has proved to exert synergistic action hence the various combinations have been tried.

Studies on tissue compatibility (eg) CSF indicate that buprenorphine and Midazolam may safely be adminsiterd epidurally and intrathecally. The use of neuraxial additive drugs have shown that this method of Pain relief provide prolonged segmental analgesia without systemic side effects of narcotics or the sensory, motor or autonomic block seen with regional anaesthetic techniques for pain relief[3].

Since many orthopaedic operations are performed frequently under sub arachnoid block it was decided to assess and compare the post-operative analgesia and side effects of buprenorphine and midazolam co-administered separately with subarachnoid anaesthetic agents like bupivacaine where longer duration of pain relief is required.

AIM OF THE STUDY

To evaluate the Post –operative analgesic effects of Intrathecal Bupivacaine with Buprenorphine and Intrathecal Bupivacaine with Midazolam following orthopaedic surgeries(lower limbs).

The parameters that were analysed are

1. Duration of analgesia
2. Quality and adequacy of analgesia as per the visual analog scale
3. Effects of Drugs on Cardio-Respiratory and Central Nervous System
4. Undesirable side effects like Motor Weakness, Urinary retention, nausea and vomiting, Neurological dysfunction and allergic reaction(like pruritus)

METHODS OF POST-OPERATIVE PAIN RELIEF

Post –operative pain is an acute pain which starts with the surgical trauma and usually ends with tissue healing.

Techniques of Post -operative Analgesia

Peri operative pain is divided in to three phases[4]

1. Intra-operative pain
2. Early post –operative pain: this is a sharp acute pain requiring potent analgesia and lasts for 1-4 days by which time endogenous opioid secretion takes place .
3. Late Post-operative pain-This is a dull continuous pain.

The various modalities available for post –operative pain relief are

I. Opiates

i. Intramuscular

ii. Continuous/intermittent intravenous

iii. Patient controlled Analgesia(PCA)

iv. Intrathecal/Epidural

v. Others

II. Non- Narcotic

Invasive

i Local Anaesthtic infiltration

ii. Regional Anaesthesia

iii. Cryoanalgesia

iv. Continuous intrapleural infusion

III. Non –Invasive:

i. Inhalational

ii. Transcutaneous electrical nerve stimulation

iii. Hypnosis

iv. Electro –Acupuncture

v. Relaxational techniques.

Any technique to be efficient must start before the onset of pain and continue throughout the duration of pain.

I. Opiates

Opiates have remained the cornerstone for management of moderate and severe pain.

i. Intramuscular Opiates

The Commonest mode of administration remains intermittent, intramuscular administration with the interval up to 8 hours. This results in oscillation of plasma levels between supra-analgesic peaks associated with toxic effects and sub-analgesic troughs associated with pain.

Agents	Bolus Dose (mg)	Receptor	Duration (Hr)
Morphine	10	Mu	3.4
Pethidine	100	Mu	3
Buprenorphine	0.3	Mu	8
Fentanyl	0.1	Mu	1-2
Pentazocine	30-60	Sigma	<3

ii. Continuous / Intermittent Intravenous

Mathers and Cousins described the concept of Minimum effective concentration(MEC) of an analgesic in blood based on Pharmacokinetics. Loading dose of the analgesic =(VDSSxMEC) mg. It is infused over 15-16 mts

Maintenance infusion=(clearancexMEC)mg/hr.

iii. Patient controlled Analgesia(PCA)

In 1971 Sechzer described the demand analgesia concept in which the patient is given small increments of morphine on demand. This had high degree of patient satisfaction and significantly low total drug usage.

A simple device is Cardiff Palliator and one demand analgesia computer. Overdosage and respiratory depression will be less likely with PCA.

iv. Spinal/ Epidural opioids:-

The Potency of analgesia by these routes results from action of the opioid on inhibitory dorsal horn opioid receptors[5].

DOSAGE SCEHDULES FOR SPINAL(EPIDURAL OPIOIDS)

Drug	Epidural Dose (mg)	Intrathecal Dose (mg)	Duration (Hrs)	Side effects	Respiratory Depression	Comment
Morphine	1-10	0.1-0.5	12-24	itching, nausea, vomiting, micturition difficulties	Yes	Slow onset delayed respiratory depression
Pethidine	50-100	10-30	3-6	Itching, nausea, vomiting and sedation	Yes	Marked sedation
Fentanyl	0.025-0.015	0.02-0.1	2-8	Itching, nausea and vomiting	Slight	
Buprenorphine	0.06-0.3		19	Itching, nausea and vomiting	Rare	

Side effects of spinal/epidural opioids

	Side Effects	Treatment
a. Common	1.Nausea and vomiting	Antiemetics
	2.Pruritus	Metoclopramide

	3.Urinary retention	Antihistamines
	4.Sedation	Cathetrisation
b.Rare and serious	Respiratory depression	Ventliation
c.Less common	Neurological risks arachnoiditis	Naloxone Doxapram

v. Other Routes of administration of opiates

Oral: MST is a continuous sustained release preparation of morphine.If gastric motility is present. It gives analgesia for up to 24 hrs comparable to i.m administration but absorption is erratic and side effects troublesome. OTEC (oral transmucosal fentanyl citrate) is available as a lollipop candy.

Sublingual: Buprenorphine 02-0.4 mg in the form of tablet is highly effective and convenient. But it has ceiling effect on analgesia and it has slow onset(three hours) of action.

Transdermal: Analgesia with fentanyl patch100-200 mcg lasts upto two hours.

Rectal: MHS (Morphine hypogel suppository) is useful in paediatric patients but has very erratic absorption.

II.Non-Narcotic Techniques

A.Invasive Techniques:

a. **Continuous Epidural Adminstration of Local Anaesthetics** Repeated doses or continuous infusion or even PCA administration of local anaesthetic can be used for post-operative analgesia.

Advantage: Profound analgesia with no respiratory depression.

Disadvantages: Tachyphylaxis, toxic effects of local anaesthetic drugs catheter migration causing total spinal block, symphathetic blockade causing hypotension and contraindication in patients on anticoagulants.

b. **Continuous Intrathecal Infusion**: Continuous infusion of local anaesthetics via 32 S.W.G. Catheter introduced through a No.29LP needle has been described but the prohibitive costs as well as technical difficulties should be quiet apparent.

c. **Other Epidural Drugs**: Midazolam 5 mg gives analgesia lasting 12 hours. Drowsiness is reported but becomes less significant after 2 hours. Calcitonin 100mcg with lignocaine and adrenaline produced good analgesia. It acts through serotoninergic pathways.

d. **Local Nerve Blocks**: Commonly used in post-operative analgesia are: Intercostal nerve block for upper abdominal and thoracic surgery.Illioinguinal andIlliohypogastric block, brachial plexus block, continuous nerve sheath block and simple incision infiltration with bupivacaine.

e. **Intrapleural Infusion**: It gives excellent analgesia but the large doses utilized (30mlof 0.5% bupivacaine) result in significantly high blood levels associated with toxicity.

f. **Cryoanalgesia**: It is ideal for post throracotomy and subcostal or flank incision. The nerve is cooled to-20degree °C with a liquid nitrogen probe. It causes axon destruction with preservation of nerve sheaths.

Advantages: Excellent analgesia lasting for days with no side effects.

Disadvantages:No analgesia to surgical drain sites, prolonged anaesthetic patch, specialized equipment required.

Non-Invasive Techniques

a. **Inhalation**: Nitrous oxide inhalation can be used in post-operative ventilated patients. Beyond 36-48 hours it can cause bone marrow depression.

b. **Transcutaneous Electrical Nerve Stimulation(TENS)**:An asymmetric biphasic waveform of 12-20m Amp and stimulation frequency is delivered. The electrodes are applied on either side of the incision and stimulation started immediately in the post-operative period.

Advantages: are low cost and no side effects. Disadvantages; are incomplete analgesia but it remains a very useful adjuvant to opiates and can lower the dose required.

c. **Electroacupunture**: The disadvantages of this procedure are specialized equipment and technical skill are required and analgesia may be inadequate.

d. **Other drugs**:Non-steroidal anti-inflammatory drugs(NSAIDS)such as aspirin, ibuprofen are useful adjuvants in children and very useful for late post-operative pain. But they inhibit gastric cyclo-oxygenase causing bleeding and ulceration. Decreased platelet aggregation and coagulation may cause increased wound bleeding.

e. Newer Drugs:

Ketorolac Tromethamine: This is a peripherally acting non opioid, nonsteroidal analgesic.It inhibits pain by inhibiting prostaglandin synthesis.

Dose: Injection ketorolac 30 mg (im) 6-8 hourly (or) Tablet ketorolac 10-30 mg 6 hourly.

Side effects: Nausea, vomiting , somnolence, hyperkinesia and myalgia.

Nefopam: This is a cyclised analog of diphenhydramine with a unique central action.

Dose: Tablet NefoPam (30mg)30-60mg 6 hourly or injectionNefopam 20 mg(im) 4-6hourly or slow (i.v)4-6hourly

Side effects: Nausea, vomiting , drowsiness, insomnia and headache.

Ketamine:A Phencyclidine derivative, which causes profound analgesia without respiratory depression.

Clonidine: Alpha 2 adrenergic agonist used orally can augment spinally mediated opioid analgesia whereas epidural or intrathecal clonidine can provide effective analgesia alone.

Intrathecal Neostigmine: Provides analgesia by inhibiting breakdown of acetylcholine, an endogenous spinal neurotransmitter. Analgesia and side effects are dose dependent.

Intra-articular Analgesia: by Morphine,and intra articular bupivacaine provide analgesia following arthroscopic and other joint surgery.

Noise: Random noise has been used to reduce pain during dental surgery. Music has been used in the management of post-operative pain and the effects probably partly due to distraction[6,7].

ANATOMY

The bony spinal canal extends from the foramen magnum to the sacral hiatus. It is joined inferiorly by the border of vertebrae, laterally by pedicles and posteriorly by the laminae and spines. The only opening in the canal are the intervertebral foramina which permits the passage of the segmental nerve and the blood vessels.

The contents of the canal are:

1. Roots of spinal nerve
2. Spinal membranes with enclosed cord and CSF.
3. Venousplexus and alveolar tissue of extradural spaces.

The Spinal Cord

The spinal cord is an elongated cylindrical mass of nervous tissue 4m in length occupying the upper 2/3 of vertebral canal. At its rostral end, it is continuous with medulla oblongata and below ends in conus medullaris, from the apex of which filum terminale interna descends with dura and arachnoid mater to the level of 2nd sacral vertebra. It pierces the dura and arachnoid and continues below as filum terminale externa, eventually blending with the periosteum on the back of coccyx.

Spinal nerves emerge from spinal cord in pairs. 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and one pair of coccygeal nerve. The spinal nerve composed of anterior and posterior roots, each with the 3 meningeal coverings cross the extradural space and unite in the intervertebral foramina to form the spinal nerve trunks which soon divide into anterior and posterior primary division and mixed nerve. These nerve roots within the duramater have no dural sheath and are therefore easily affected by doses of analgesic drugs brought into contact with them.

Vascular supply of the spinal cord

One anterior and two posterior spinal arteries on each side arise from the postero-inferior cerbellar artery at the base of the brain. They supply part of the posterior horn and posterior

column of spinal cord and replenished by numerous segmental arteries, the posterior radicular arteries. There is only a single anterior spinal artery arising from the union of a small branch from each vertebral artery. The anterior and posterior spinal arteries do not anastomose with each other. The spinal veins form anterior and posterior plexuses, which drain into the vertebral azygos and lumbar veins.

Indentification of spinal verterbral level

1. The line joining the illiac crest passes through the L4 vertebra (or) L4-L5 space.

2. A line drawn between the joints where the lateral edge of the erector spinae muscles meet the lower border of the 12th rib. This line passes through the lower border of L1 spinous process.

3. With the arm by the sides, the horizontal line joining the lower border of both scapulae pass usually though T7 vertebral space.

Structures pierced while performing a subarachnoid block

Skin

Subcutaneous tissue

Supraspinous ligament

Inter spinous ligament

Ligamentum flavum

Duramater

Pain Pathways

Pain receptors appear to consist of peripheral plexus of unmyelinated nerves, activated by high intense stimuli which may be, thermal, chemical (or) mechanical. Pain is conducted along two types of fibres in the periphery, `A' delta and `C' fibres. `A' delta fibres are rapidly conducting (12-30 metre/sec). They appear to conduct the sharp pain produced by pinprick (or) electrical stimuli. `C' fibres are very fine un-myelinated fibres which conduct at a very slow rate of 2-3 metres/sec. their threshold for stimulation is higher than that of `A' delta fibres.

Peripheral sensory neurons have their cell bodies in the dorsal root ganglia and the Central projections of the `A' delta and `C' fibres enter the dorsal horn in the lateral division of the dorsal root. `A' delta and `C' fibres terminate principally in the marginal layer (Lamina-I) and substantia gelatinosa (Lamina II). Some of the neurons of Lamina I synapse with `A' delta columns without synapsing with neurons from the deeper layers. The majority of fibres synapse with substantia gelatinusa and send projection to deeper layers (or) synapse with the dendrites of neurons whose cell bodies reside in deeper layers principally in Lamina V.

The central projections form cell bodies in Lamina IV, V and VI with a contribution from Lamina I cross the midline in the anterior commissure to form spino-thalamic tract, which ends in the thalamus. The ventro-posterior nucleus of the thalamus projects to the post-central gyrus, the sensory cortex where the anatomical representation is reasonably precise. While it appears that the thalamus is involved in the experience of pain, the post-central gyrus is necessary for its accurate localisation and prefrontal cortex for the unpleasant affective reactions to it.

PHYSIOLOGY

Physiology of pain

The transmission of pain has four distinct physiologic processes.

1. **Transudation**: Conversion of noxious stimuli into electrical signals by peripheral

afferrents.

2. **Transmission**: Propagation of electrical signals along the nociceptive pathways

3. **Modulation**: Alteration of the nociceptive signal within the dorsal horn.

4. **Perception**: Nociceptive input is integrated with cognitive and emotional factors to create subjective pain.

Intrathecal space

Spinal anaesthesia may be defined as the temporary interruption of transmission of nerve impulses produced by the injection of local anaesthetic agents into the spinal space. Sites of action of local anaesthetics placed in the subarachnoid space in order of importance are

1. Primary- on nerve roots of spinal cord.

2. Secondary –on dorsal root ganglia and postero- anterior horn synapse.

3. Limited and incomplete – in spinal cord parenchyma on ascending – descending tracts.

Direct effects of Local anaesthetics injected into subarachnoid space:

When the nerve roots are exposed to an anaesthetic solution the blocking action is primaril a function of fibre size.

Susceptibility depends on

1. Fibre size
2. The degree of myelinization and the distance between the nodes of ranvier.
3. Frequency of nerve impulse transmission.

Generally local anaesthetic agents block transmission most easily in the smaller fibre, such as the thinly myelinated B fibre carrying symphathetic impulses and the non-myelinated

C fibres carrying pin-prick sensation. Block of the A fibres, the large motor fibres and medullated proprioceptive fibres is slow in onset and of shorter duration . They are the last to be blocked.

Sequence of Nerve modality Block

Observation of a patient after spinal block will reveal the sequence of block of the various nerve modalities as

1. Vasomotor block- dilation of skin vessels and increased cutaneous blood flow
2. Block of cold temperature fibres.
3. Sensation of warmth by patient.
4. Temperature discrimination is lost.
5. Slow pain.
6. Fast pain.
7. Tactile sense lost.
8. Motor paralysis –extensor muscles are affected before the flexor muscles
9. Pressure sense abolished
10. Proprioception is lost.

During recovery anaesthesia recedes from head and feet areas towards the midline (i.e) a point near the site of anaesthetic agent is the last to recover.

Opiate receptors

Opiates produce their action through specific recognition sites (or) receptors. Opiate receptors are wide spread in the brain stem and spinal cord. They are found in areas associated with the emotions,the amygdala and limbic system, in the area postrema associated with stimulant effect upon the chemoreceptor trigger zone and along the course of pain pathways in the medial thalamus, in the periaqueductal gray matter and in the substantia gelatinosa of trigeminal nerve, spinal cord and the gastro- intestinal tracts.

The possible mechanism of action of these exogenously administered opioid may be by[8]

1. Stimulation of the stereo specific receptors.

2. A local anaesthetic like action on the surface of excitable cell membrane that does not involve a stereospecific receptor (opioid agonists)

3. Blockade of the neuron excitability by a mechanism which hyperpolarizes the cellular membrane and make them more difficult to depolarize and thus decreases neuro-transmission.

Classification of opiate receptors:

Martin and coworkers (1976) proposed three classes of opiate receptors based on the studies on dogs with morphine and some benzomorphin derivatives-M(Mu) receptors. Kappa receptors and sigma receptors. To this the Kosteshitz classification would add delta receptors to explain certain selective effects of Leu enkephalins.

Mu receptors:

The MU receptor is a major antinociceptor site located in both the brain and spinal cord with highest concentration in the periaqueductal grey matter and substantia gelatinosa respectively. Opioid induced analgesia at the MU receptor is dose dependent. Morphine is a typical agonist at this receptor. The MU receptor is thought to mediate supra analgesia, respiratory depression, euphoria and physical dependence.

Mu receptor have been further classified in to

Mu1-Those with high affinity –mediate analgesia

Mu2-Those with low affinity –not associated with analgesia.

Respiratory depression is probably through Mu2 receptor.

Kappa receptor

Ketocyclazocine and ethyl ketocyclazocine were proposed as Kappa agonists and have a greater effect on spinal nociceptive responses than supraspinal response although the kappa receptor agonists were associated with sedation and miosis.

Sigma receptor

Interaction with proposed sigma receptor was not associated with reduced response to noxious stimuli but associated with mydriasis, tachycardia and mania, subsequently these receptors have been associated with the pshycomimetic action of many opioid derivatives. A typical agonist is N allyl norcyclazocine. Respiratory and vasomotor stimulation were also observed on interaction with this receptor.

Delta receptor

Studies in guinea pig brain using methionine and leucine enkephalin suggested another opioid receptor which is designated the delta receptor. At this receptor stable enkephalin analogue D Aladien Enkephalin(DADL)has greater activity than Mu agonist drugs.

Epsilon Receptor

At this receptor electrical stimulation are blocked by beta endorphins, a stable peptide with opioid activity, found mainly in the pituitary.

Endorphins and Enkephalins

Endogenous opioid activity in brain and pituitary extracts was described soon after the discovery of opioid receptor. Two pentapeptides with opioid activity were isolated from the brain and named as Enkephalins and are further classified into Met -enkephalin and Leu-enkephalins. Subsequently other polypeptides were identified namely endorphins which are of four types namely alpha, beta, delta and gamma endorphins. Beta endorphin is widely distributed but found principally in hypothalamus where it is passed via long axons to third ventricle after release into CSF. Beta

endorphins can act on opioid receptor in the brain stem and spinal cord. Beta endorphins appear to possess all the activity of morphine producing analgesia, euphoria, behavioural effects and hypoglycemia and to be equipotent on all opioid receptors.

Sites and Mechanism of action of opioid induced analgesia:

In 1979, Wang et al reported remarkable pain relief using subarachnoid morphine in cancer patients with demonstration of opiate receptors in the spinal cord and segmental analgesia from intrathecal opiates in rats. Many clinical trials of their use in the treatment of post-operative, chronic and obstetric pain were performed.

Spinal opiates administration produce segmental analgesia, the extent and spread of which is dependent on site of injection and position, while the duration is little longer than that produced by bupivacaine. Yakash and Rudy showed that the potency and duration of analgesia of the Mu agonists- fentanyl, morphine and pethidine given intrathecally to rats corresponds to the systemic properties and that the kappa and partial antagonists pentazocine, cyclazocine were ineffective.

In man opiates have been used successfully chiefly in the treatment of chronic pain, post-operative and obstetric pain. Neither analgesia nor side effects are likely to result from systemic absorption of spinally administered opioids. Intrathecal morphine is effective in a dose well below that required for systemic effects while analgesic effect generally correlates poorly with plasma concentration following epidural fentanyl, pethidine and morphine.

Intrathecal opiates can gain access both to the substantia gelatinosa in the cord and the respiratory and vomiting centre via the CSF. Epidurally administered agents however have two possible routes

of access to the cord -one via CSF and the other via axonal transmission.

A comparison of action and efficacy of spinally applied opioid and local anaesthetic agents:

	Actions	Opioids	Local Anaesthetics
a.	Site of Action	Substantia gelatinosa of dorsal horn of spinal cord.	Nerve roots (and long tracts in spinal cord).
b.	Type of blockade	Presynaptic and (post synaptic) inhibition of neuronal cell excitation.	Blockade of nerve impulse conduction in axonal membrane.
c.	Modalities blocked	Selective block of pain conduction	Blockade of sympathetic pain fibres often also loss of sensation and motor function.
Type of pain and efficacy of blockade			
a.	Surgical pain	Partial relief	Complete relief possible
b.	Labour pain	Partial relief	Complete relief
c.	Postoperative pain early first 24 hours	Fair relief (High dose)	Complete relief
	24 Hours +	Good relief (low dose)	Complete relief
	Chronic pain	Good relief	Impracticable

GABA Receptor

Midazolam when given intrathecally produces analgesia by acting on spinal GABA receptors. There are two types of GABA receptors **GABA** A and **GABA** B. Midazolam binds to the alpha subunit of the pentamer GABA A receptor leading to conformational change, causing increased chloride ion conductance and hyperpolarisation and thereby acts by potentiating the inhibitory neuro transmitter GABA. This is mostly a post synaptic action while GABA B receptors mainly have pre synaptic antinociceptive effect by decreasing the excitatory neuro transmitter release.

Intrathecal Midazolam positively modulates GABA A/ Benzodiazepine receptor complex causing the release of an edogenous opioid acting at opioid receptors and also intrathecal midazolam causes antinociception, by combining with three different receptor sub types of GABA A in the spinal cord[9,10].

PHARMACOLOGY

BUPRENORPHINE

Buprenorphine Hydrochloride is a semi synthetic derivative of morphine alkaloid, thebaine and is highly lipophilic (opioid) with a strong analgesic and marked narcotic antagonist activity. It is 20-50 times more potent than Morphine. Buprenorphine has molecular formula C_{29} H_{41} NO_4 HC1 with a molecular weight of 5049.

PHARMACOLOGICAL ACTION AND SIDE EFFECTS

Buprenorphine in a single intramuscular dose of 0.3mg relieved pain for up to 6 hours. Higher dose (up to 0.6mg) did not provide, significantly greater pain relief. Houde et al 1976 reported that (intramuscular) Buprenorphine was about 28 times as potent as morphine in analgesic activity.

It produces analgesia by modifying the emotional reaction to pain and by raising the pain threshold. It also provides sedation and hypnosis.

NARCOTIC ANTAGONISTIC ACTIVITY

Houde et al (1976) proved in patients receiving chronic (about 18 days) high doses (gradually increasing doses up to 8mg intramuscular daily by day 14). Buprenorphine HCL treatment, the effect of single dose of 15-20 mg of Morphine were blocked.

The antagonistic activity of Buprenorphine Hcl also has been demonstrated following fentanyl (or) Sufentanyl anesthesia, where Buprenorphine has been used to reverse anaesthetic effects[12].

RESPIRATORY EFFECTS

Respiratory depressant activity of buprenorphine appears to reach a ceiling at a dose of about 0.6 to 1.2 mg (im (or) (iv). Respiratory depression is slow in onset (peak effect 3 hours after administration) and last longer (upto 7 hours) (Goodman, Gillman"). The significant decrease in minute volume, which (occurred) 1 hour after (iv) 0.3 mg was rapidly (but temporarily) antagonised by IV injection of a single dose of respiratory stimulant doxapram 0.5 - 1mg/kg (225mg over 2 hours). Very high doses of naloxone produced only partial reversal of respiratory depression.

In spontaneously breathing anesthetised patients, intramuscular dose of 3 and 4 mcg/kg buprenorphine decreased both the respiratory rate and volume.

CARDIO - VASCULAR EFFECTS

Buprenorphine produced reduction in heart rate (10%) and decrease in systolic blood pressure (5-10%) with only minor decrease in (diastolic) pressure, central venous pressure, cardiac index, stroke index, and left vertricular work decreasing by about 12 to 17%.

DEPENDENCE LIABILITY STUDIES

There are two kinds of dependence associated with drugs acting at narcotic receptors - pshycic and physical. Buprenorphine hydrochloride has a much lower dependence liability than morphine.

Withdrawal symptoms were mild to moderate and they demanded drugs for relief. However, Mello and Mendelson (1980) reported in their experimental subjects no withdrawal symptoms upon abrupt withdrawal.

PHARMACOKINETIC STUDIES

Absorption

Well absorbed by most routes including the sublingual 0.4 to 0.8 mg and the concentration in the blood peaks within 2 hours and allows absorption directly into the systemic circulation.

Distribution

Highest levels of radioactivity was found in liver both after oral and (im) injection but peak levels in this organ occurred (10mts) after an oral than after an (im) (40mts) dose. It crosses placenta and appears to accumulate in the foetal gastrointestinal lumen.

Protein Binding

The drug is highly protein bound (about 96%) primarily to alpha and beta globulin fraction.

Metabolism

Buprenorphine hydrochloride is conjugated with glucuronic acid during passage through the gut wall. In the bile it is present as glucuronide conjugate of buprenorphine hydrochloride as, N-De alkyl Buprenorphine but the CNS contains only unconjugated drug suggesting that the effects of buprenorphine are mediated by interaction of the drug alone with opiatereceptors.

Excretion

Excreted mainly in faeces unchanged with smaller amounts appearing in urine (N-de alkylated and conjugated metabolites). The preservative free Bu-Prenorphine available as 0.3 mg/ml ampoules was used for this study.

MIDAZOLAM

Midazolam is a water soluble imidazo benzo- diazepine and its unique feature being its PH dependent imidazole ring which opens at PH<4, and accounts for its water solubility in aqueous solution and rapid metabolism at PH>4, the ring closes leading to an increase in lipid solubility.

DOSAGE AND ROUTES OF ADMINISTRATION

Routes

Oral, nasal, intramuscular, intravenous, intrathecal and Epidural.

Dosage

Sedation	-	0.05 - 0.1 mg/kg
Premedication	-	0.07 - 0.08 mg/kg
Induction	-	0.1 - 0.3 mg/kg
Infusion	-	2.5mg / kg/ hr
Intrathecal	-	0.3 - 2 mg
Epidural	-	0.1 - 0.2 mg/kg

Mechanism of pain relief in central Neuraxial blocks

Midazolam causes antinociception by combining with three different receptor subtypes of GABA (A) in the spinal cord.

Intrathecal midazolam positively modulates GABA (A) / benzodiazepine receptor complex causing the release of an endogenous opioid acting at opioid receptors.

Central nervous system

Decreases cerebral blood flow, cerebral oxygen requirement and intracranial pressure.

Sedation, hypnosis, anxiolysis

Anterograde amnesia, Anticonvulsant

Respiratory system

Transient apnoea occurs when administered in doses greater than 0.15 mg/kg and in opioid premedicated subjects. Potent respiratory depressant, especially in Chronic Obstructive Pulmonary disease (COPD) patients.

Cardio-vascular system

Decrease in peripheral vascular resistance and transient attenuation of baro-receptor reflexes leading to hypotension and tachycardia is seen. In hypovolemic and elderly patients there is increased risk of significant hypotension.

Local effects

No venous irritation and thrombophlebitis.

Pharmacokinetics

It has a PH of 3.5 with pka of 6.15

Protein binding 96-98%

Volume of distribution: 1 - 1.51kg

Clearance: 6-8ml/kg/mt

Elimination half time - 1.4 hr., increased in elderly and obesity.

Metabolised by hepatic micro somal enzyme cytochome. P 450 by hydroxylation to 1.0 H and 40H derivatives.

Excreted in urine as glucuronide conjugates. Erythromycin decreases its hepatic clearance leading to increased duration of action. <0.02% is excreted unchanged, therefore it is

not affected by renal failure. The preparation used in this study was preservative free midazolam available as 5mg/ml ampuoles.

Bupivacaine

It is an amide type local anaesthetic, synthesized in Sweden by Ekenstan and colleagues in 1957. The Pka is 8.1 with molecular weight of 288 and protein binding of 96% being more Cardiotoxic (than lignocaine) because of its avid binding to cardiac muscle. It causes less motor blockade than (lignocaine). It is 4 times as potent as the latter because of its high lipid solubility.[8]

Mechanism of Action

In its unionized form, it enters the cell and after ionization binds to the interior of the sodium channels causing sodium channel blockade leading to inhibition of propagation of nerve action potential.

PHARMACODYNAMICS

Central nervous system

It exerts biphasic effect with initial excitation followed by depression of the central nervous system.

Irritability, restlessness, confusion and convulsion followed by stupor, coma and death.

Cardio-vascular system

It is a potent cardiotoxic agent because of its slow dissociation from the cardiac muscle. Hence it is contra-indicated for intravenous regional analgesia. It causes bradycardia and cardiac arrest following intravenous injection.

Pharmacokinetics

It has a slow onset of action of 15 minutes with prolonged duration of action depending on mode of administration. It is bound to acid glycoprotein, metabolised by N-de alkylation to its metabolite pipecolyloxylidine that is excreted renally. 16% excreted unchanged renally.

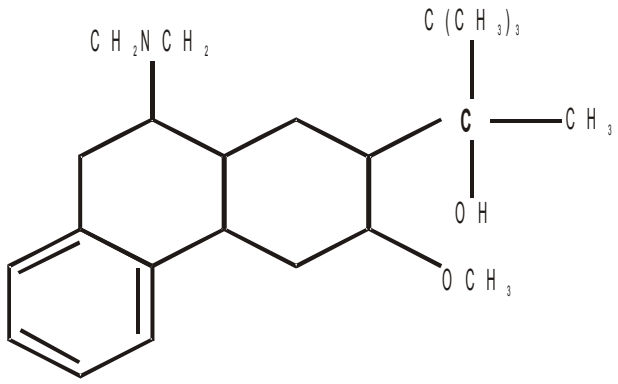
Volume of Distribution - 0.471 kg. The plasma level of Bupivacine following intrathecal analgesia is 1-1.4g/ml.

The preparation used for this study was 0.5% Bupivacaine (heavy) available as 4ml ampoules (Preservative free).

Structural formula

1 Butyl 1-2 piperidyl 1 forma 2-6 xylidine hydrochloride monohydrate C_{18} H_{28} N_{20} HCL H_20.

BUPRENORPHINE



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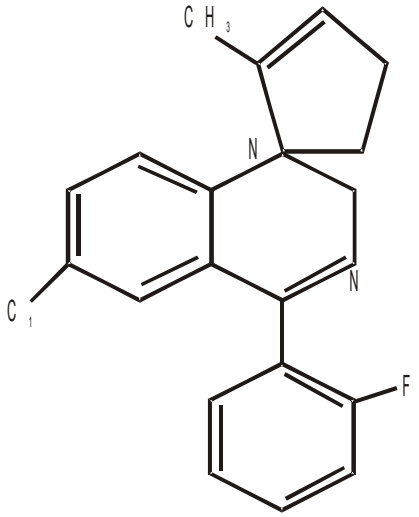
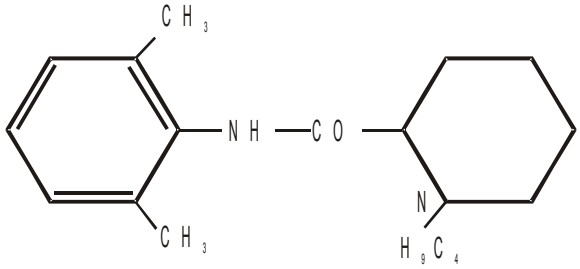


B U P I V A C A I N E



REVIEW OF LITERATURE

Extracted from the POPPY, the opium alkaloid was named morphine after the Greek goddess of sleep, Morphina (also the Greek god of dreams, Morphews) in 1803 by Fredrich Meisuer.

1. Synder (1973) discovered the opiate receptors in the dorsal horn of spinal cord, the lower medulla and the floor of the fourth ventricle and initiated the idea that subarachnoid injection of opiates could provide good analgesia

2. Huges et al (1975), the discovery of enkephalins and complex endogenous opiod systems initiated the opiod receptor theory and study of pain mechanisms.

3. Yakash and Rudy studied the spinal action of morphine in animals, the pain relief was attributed to the spinal analgesia caused by direct action of narcotics on specific opiate receptors.

4. Kay B (1978), studied the double blind comparison of the effects of morphine 10 mg IV and buprenorphine 0.3 mg IV in the prevention of pain after operation. The drugs were given by the anaesthetist at the end of surgery and the onset and severity of pain were assessed by a trained nurse. He found that with buprenorphine the pain relief was far more than twice that of morphine. The only side effect noticed was drowsiness. The incidence being greater after buprenorphine that after morphine.

5. Wang et al (1979) reported the first use of intrathecal opiates in man. They studied 8 patients with intractable pain due to cancer of genito urinary tract with invasion of lumbosacral plexus. They injected 1 mg and 0.5 mg of morphine intrathecally and reported that the duration of pain relief ranged from 12-24 hours.

6. Cousins MJ and Glynn GJ (1979) reported the evidence of selective action of spinal narcotics. They found that 2 mg of Intrathecal morphine gave a pain relief of 24 hours after surgery. The absence of changes in sensory motor and sympathetic function indicates that this form of analgesia may have considerable advantage over other methods for the relief of severe chronic and acute pain in man.

7. Budd K. (1981) studied (IV) buprenorphine to produce analgesia in the immediate post operative period, the dose being titrated against the response of each patient in order to obtain complete freedom from pain. In 50 patients following LSCS under general anaesthesia, buprenorphine in the dose range 0.4 – 7.0 mg was found to be a potent, long lasting and safe analgesic. Serial blood gas estimations performed on ten of the patients confirmed the clinically observed lack of respiratory depression.

8. Watson and co-workers (1982), who found a longer duration of analgesia with buprenorphine 0.6 mg that 0.3 mg given IV after surgery. Analgesia and hormonal effects were greater with the greater dose without a parallel increase in respiratory depression.

9. Egan Lanz et al (1984), in their double blind study of post – operative analgesia, 158 patients who were given epidural analgesia with mepivacaine or bupivacaine with buprenorphine for orthopaedic surgery of lower extremities found that analgesia after 0.15 mg of Buprenorphine was superior to that after no injections for 6 hours after surgery. 0.3 mg of buprenorphine was superior both to no injections and to 0.15 mg of buprenorphine until 12th hour without any evidence of late respiratory depression. They concluded that epidural administration of 0.3 mg of Buprenorphine may be recommended for post operative analgesia following orthopaedic surgery of lower

extremities.

10. Green DW et al (1985), in a randomized double blind trail comparing morphine and buprenorphine and post operative analgesia combined with droperidol was conducted in 60 patients. Compared with morphine, taken as the standard analgesic, buprenorphine was shown to be a satisfactory analgesic for major surgery with no difference in incidence of unwanted effects.

11. Wolff J et al (1986), in a double blind controlled study, epidural buprenorphine 0.3 mg was compared with 4 mg of epidural morphine for post operative pain relief in the first 24 hours after major orthopaedic surgery. Duration of action was 620 minutes with buprenorphine with no side effects and 580 minutes with morphine with pruritis and urinary retention.

12. Lipp M et at (1987) in a double blind, randomized study of 29 patients who underwent orthopaedic procedures with the additional effect of intrathecal buprenorphine on isobaric spinal anaesthesia and post operative analgesia. The injections were 20 mg tetracaine (19 patients) or 20 mg tetracaine plus 0.15 mg buprenorphine (10) patients. After buprenorphine patients became aware of pain sensation 13 hours after injection; in the control group pain free intervals lasts only 9 hours. There was no alteration in blood pressure and pulse rate was slightly diminished with buprenorphine group.

13. Capogna et al (1988), studied intrathecal 0.03 mg buprenorphine with bupivacaine 30 mg for post operative analgesia in the elderly patient showed prolonged analgesia with minimal disturbance of consciousness and comfortable breathing. The only side effects were nausea and vomiting in 11 and 14 patients respectively.

14. Calleno D et al (1989) spinal buprenorphine for post operative analgesia after ceasarian section. Group A (controls n = 15) received hyperbaric bupivacaine; group B and C received the same but with the addition of 0.03 mg or 0.045 mg buprenorphine, respectively. Patient receiving higher dose had longer effect of 420 minutes than lower dose of 173 minutes analgesia without any increase in side effects.

15. Sen M (1992) studied intrathecal buprenorphine for post operative analgesia in orthopaedic surgery. Intrathecally either hyperbaric bupivacaine 1 ml in group A (30 cases) or bupivacaine 1 ml and buprenorphine 300 micrograms in combination was given, only minimal disturbance of consciousness and respiration were observed. The only side effect of buprenorphine group was nausea and vomiting in 10 patients.

16. Nishimi et al (1994) studied the effect of intrathecal administration of opioid on minimum alveolar concentration and postoperative pain relief a comparison of morphine and buprenorphine showed:

- Intrathecal administration of 0.05 mg and 0.075 mg of buprenorphine has shown analgesic effect without any side effects.
- With morphine 0.5 mg there was adequate post – operative analgesia with severe pruritus

17. Lundborg et al (1999), studied Intrathecal pain management for progressive systemic sclerosis with long term continuous intrathecal buprenorphine / bupivacaine concluded intrathecal infusion of buprenorphine / bupivacaine provided satisfactory long term pain relief in a patient with PSS associated raynauds phenomenon, skin ulceration and intractable ischaemic pain.

18. Batra YK. et.al (1999) conducted a randomized study in 30 patients undergoing knee

arthroplasty to study the analgesic efficacy of intrathecal Midazolam with Bupivacaine. They used 2 mg Midazolam and concluded that addition of Midazolam to Bupivacaine intrathecally provided better post operative analgesia without any adverse effects.

19. M.H. Kim et. Al (2000) conducted a double blind study to evaluate post operative analgesic effects of intrathecal Midazolam with Bupivacaine for haemorrhoidectomy in 45 patients (3 groups – 15 patients in each group) while control group received 1 ml of 0.5% heavy bupivacaine plus 0.2 ml of 0.9% saline intrathecally. The other two groups received 0.2 ml and 0.4 ml of Midazolam along with 1 ml of 0.5% Bupivacaine heavy and concluded that the time for first demand analgesia was significantly greater in the study group.

20. Nishiyama et.al (1999) conducted a study to find out the spinal analgesic interaction between Midazolam – benzodiazepine – GABAA receptor agonist and AP5 N methyl D aspartate (NMDA) receptor antagonist were tested for their tail withdrawal response by tail flicktest after intrathecal administration. They concluded that spinally administered Midazolam and AP5 exhibited potent synergistic analgesia and acute thermal nociception in rats.

21. Valentine. JM. et.al (1996) conducted a randomized clinical trial in 52 patients scheduled for caesarian section under spinal anesthesia with (1) Bupivacine heavy 0.5%, 15mg + 1.2 ml 0.9% saline, (2) Bupivacaine 0.5% heavy 15mg, 0.2 mg (0.2 ml) diamorphine + 1 ml of 0.9% saline (3) Bupivacaine heavy 15mg, 0.2 ml (0.2 mg) diamorphine and 1 mg (1ml) Midazolam. They concluded that Midazolam has antinociceptive effect at spinal level and their study showed statistically significant but clinically marginal effect.

22. Good child C.S. et.al (1996) conducted experiments in rat and found that antinociception

by intrathecal Midazolam involves endogenous neurotransmitters acting at spinal cord delta opiod receptors.

23. CS Goodchild and KM Serrao (1987) conducted a study to find out the possible analgesic effect of intrathecal Midazolam in rats and concluded that intrathecal Midazolam causes spinally mediated analgesia by binding to benzodiazepine receptors in the spinal cord and did not have a local anaesthetic action.

24. Murat Bahar (1997) conducted a study in rats and concluded that Midazolam when injected intrathecally it produces reversible, segmental, spinally mediated antinociception.

25. Kohnu T. et.al (2000) conducted a study to evaluate the site of action of Midazolam in adult rat spinal cord slices and concluded that Midazolam augments both the duration of GABA mediated synaptic current and the amplitude of GABA induced current by acting on GABA A benzodiazepine receptors in substantia gelatinosa neurons.

26. Indian Journal of Anaesthesia[2005] conducted a double blind study on 53 adult ASA grade I/II patients and concluded that intrathecal combination of midazo;am and bupivacaine provides longer duration of post operative pain relief as compared to bupivacaine alone, without prolonging duration of dermatomal sensory block

MATERIALS AND METHODS

The prospective clinical study was conducted at the Govt. Stanley Medical College Hospital, Chennai-1, in 75 adult patients undergoing elective Lower Limb Orthopaedic Surgery.

The hospital ethical committee approved this study and informed consent was obtained from each patient.

Study design

An open, randomised, comparative parallel group design was employed.

Inclusion criteria

ASA 1 & II

AGE 18-65

Orthopaedic procedures of Lower Limbs.

Exclusion criteria

ASA III & IV

Bleeding diathesis

Spinal Deformity

Age <18 years> 65 years

CNS disorder

Local anaesthetic sensitivity

Local Sepsis

Number of patients

75 adults 25 in each group

Group A received 3.0ml of (15mg) Bupivacanie (Preservative free) +0.4 ml of 0.9% normal saline.

Group B received 3.0ml (15 ml) of (Bupivacanie)+ (0.4ml) 0.12mg preservative free Buprenorphine

Group C received 3.0ml of (15mg) Bupivacanie + (0.4ml) 2 mg of preservative free Midazolam

Pre-operative preparation

The patients were explained about the procedure and informed consent was obtained. Tablet diazepam 10 mg given as preoperative night sedation. Patients were made familiar with the visual analogue scale (VAS) and were trained to use it adequately. Bupivacaine sensitivity was also tested. Informed consent was obtained. Pre operative fasting was 6 hrs for solids, 4 hrs for clear liquids. Vital signs were recorded on the day of surgery. No premedication was given to any patient on morning of surgery.

Investigations

Urine-Albumin and sugar

Haemoglobin

Bleeding time

Clotting time

Blood urea, sugar

Serum creatinine, Elecholytes

ECG and Xray chest

Anaesthetic procedure

Sub arachnoid block. On arrival at operation threatre, basic monitoring was established with ECG, NIBP and pulse oxymeter.

Intravenous line started with 18G iv canula on the left forearm and preloaded with a crystalloid 10ml/kg, prior to sub-arachnoid block. With sterile aspetic prxecautions, lumbar puncture was done with 23G quincke type spinal needle, with the patient in the lateral decubitus position at L3-L4 space and hyperbaric 0.5% bupivacane (Preservative free) + 0.4 ml of 0.9% normal saline in group A and 3.0ml of 0.5% Bupivacane with 0.12mg (0.4ml) of preservative free Buprenorphine in Group B and 3.0ml of 0.5% Bupivacaine with 2mg (0.4ml) of preservative free midazolam in Group C was deposited.

Following intrathecal injection, the patient was immediately placed in supine Position and O^2 4L/mt administered to all patients with Hudsons nasal canula.

Assessment of the patient with recording of the Data

The following variables were assessed in the operation theatre and post operative ward

1. Vital parameter like heart rate, respiratory rate, mean arterial pressure and oxygen saturation were monitored.

2. Dermatomal sensory blockade to Pin-prick was evaluated-maximum levels of impaired sensation noted.

3. Time of onset of analgesia was noted

4. Duration of sensory and motor blockade recorded

5. Pain was evaluated with visual analog scale devised by Revill and Robinson (1976) - VAS 0-100mm

0-20mm - No pain

20-40mm - Mild pain

40-60mm - Moderate pain

60-80mm - Severe pain

80-100mm - Unbearable pain

If the patient is asleep, it is taken as no pain. The time of first demand analgesia was noted.

6. Modified bromage scale for the onset of and recovery from motor block.

0	Free movement of legs and feet, with ability to raise extended leg.	None
1	Inability to raise extended leg and knee flexion is decreased but full flexion of feet and ankles is present	Partial 33%
2	Inability to raise leg or flex knees, flexion at ankle and feet present	Partial 66%
3	Inability to raise leg, flex knee or ankle (or) move toes	Complete paralysis

7. Sedation score was noted intra-operatively and post-operatively every 4 hours for 12 hours.

0 = wide awake

1 = Sleeping comfortably responds to verbal commands

2 = Deep sleep but arousable

3 = Deep sleep, not arousable

After completion of surgery, patient was shifted to recovery room and was observed in the recovery room for 2 hours post operatively, after which the patient was shifted to surgical post-operative ward.

The following parameters were observed post-operatively:

1. Pain assessment - VAS
2. Sedation
3. Heart Rate
4. Respiratory rate
5. Oxygen saturation
6. Time of first demand analgesia
7. Self voiding time
8. Time of recovery from motor block.
9. Side effects like post-operative nausea and vomiting, allergic manifestations and neurological deficit.

OBSERVATION AND RESULTS

Study Material

A total of 25 cases each were randomly allocated to one of the following three groups of study viz. Group B – 0.5% Bupivacine (Heavy) with Buprenorphine 0.4 ml (0.12 mg); Group C – 0.5% Bupivacine (Heavy) with Midozolam 0.4 ml (2 mg); Group A – control (i.e.) 0.5% Bupivacine (Heavy) preservative free 3.0 ml. +0.4 ml of 0.9% normal saline.

Table 1: Distribution of age of cases by groups[$]

Age	Gr. B	Gr. C	Gr. A	p-value
No. of cases	25	25	25	
Mean	46.7	46.0	45.2	
S.D.	10.03	10.39	10.59	0.88
Median	48	46	47	
Mode	38	48	48	
Range	26-63	26-62	22-64	
Stat. Significance	p-value			
Gr. B vs. Gr. A	0.61			
Gr. C vs. Gr. A	0.70			
Gr. B vs. Gr. C	0.80			

[$] *Not statistically significant*

The mean distribution of cases by age was observed to be generally not statistically significant between Group B and Group C as well as between the groups and control.

Table 2: Distribution of height of cases by groups[$]

Height	Gr. B	Gr. C	Gr. A	p-value
No. of cases	25	25	25	
Mean	162.9	162.8	163.3	
S.D.	4.56	4.74	2.77	0.92
Median	162	162	163	
Mode	160	161	162	
Range	155-176	155-176	159-170	
Stat. Significance	p-value			
Gr. B vs. Gr. A	0.74			
Gr. C vs. Gr. A	0.69			
Gr. B vs. Gr. C	0.95			

[$] *Not statistically significant*

The mean distribution of cases by height was observed to be generally not statistically significant between Group B and Group C as well as between the groups and control.

Table 3: Distribution of weight of cases by groups[$]

Weight	Gr. B	Gr.C	Gr. A	p-value
No. of cases	25	25	25	
Mean	64.1	63.4	63.2	
S.D.	6.51	8.99	6.04	0.89
Median	63	65	62	
Mode	60	54	68	
Range	55-80	45-82	52-76	
Stat. Significance	p-value			
Gr. B vs. Gr. A	0.61			
Gr. C vs. Gr. A	0.93			
Gr. B vs. Gr. C	0.75			

[$] *Not statistically significant*

The mean distribution of cases by weight was observed to be generally not statistically significant between Group B and Group C as well as between the groups and control.

Table 4: Distribution of cases by groups and four-hourly grade of sedation

Four-hourly grade of sedation	Gr. B		Gr. C		Gr. A		p-value
	No.	%	No.	%	No.	%	
Zero-hour							
0	8	32.0	1	4.0	21	84.0	<0.001*
1	10	40.0	16	64.0	4	16.0	
2	7	28.0	8	32.0	0	0.0	
Stat. Significance	p-value						
Gr. B vs. Gr. A	<0.001*						
Gr. C vs Gr. A	<0.001*						
Gr. B vs Gr. C	0.03*						
Four-hours							
0	0	0.0	4	16.0	25	100.0	
1	13	52.0	21	84.0	0	0.0	<0.001*
2	12	48.0	0	0.0	0	0.0	
Stat. Significance	p-value						
Gr. B vs. Gr. A	<0.001*						
Gr. C vs Gr. A	<0.001*						
Gr. B vs Gr. C	<0.001*						
Eight-hours							
0	4	16.0	23	92.0	25	100.0	<0.001*
1	19	76.0	2	8.0	0	0.0	
2	2	8.0	0	0.0	0	0.0	
Stat. Significance	p-value						
Gr. B vs. Gr. A	<0.001*						
Gr.C vs Gr. A	0.15						
Gr. B vs Gr. C	<0.001*						
Twelve-hours							
0	20	80.0	25	100.0	25	100.0	
1	5	20.0	0	0.0	0	0.0	0.005*
2	0	0.0	0	0.0	0	0.0	
Stat. Significance	p-value						
Gr. B vs. Gr. A	0.05*						
Gr. C vs Gr. A	-						
Gr. B vs Gr. C	0.05*						

The distribution of cases by four-hourly grade of sedation was observed to be significantly higher among Group B ($p \leq 0.05$) up to 12-hours and Group C ($p < 0.001$) up to eight hours than control. The grade of sedation was higher among Group C than Group B up to 12th hour ($p \leq 0.03$) . These are statistically significant.

Table 5:Mean Distribution of cases by groups and SpO2

SpO2	Gr. B *(n=25)*	Gr. C *(n=25)*	Gr. A *(n=25)*	p-value
Pre-OP				
Mean	98.4	98.3	98.6	0.54
SD	0.76	0.69	0.87	
Stat. Significance	p-value			
Gr. B vs. Gr. A	0.49			
Gr. C vs Gr. A	0.29			
Gr. B vs Gr. C	0.70			
Intra operative				
Mean	98.7	98.7	98.2	0.06
SD	0.84	0.85	0.87	
Stat. Significance	p-value			
Gr.B vs. Gr. A	0.05*			
Gr. C vs Gr. A	0.05*			
Gr. B vs Gr. C	0.87			
0-hour				
Mean	98.6	98.4	98.7	0.61
SD	0.87	0.77	0.9	
Stat. Significance	p-value			
Gr. B vs. Gr. A	0.63			
Gr. C vs Gr. A	0.32			
Gr. B vs Gr. C	0.61			
4-hour				
Mean	98.4	98.6	98.6	0.69
SD	0.82	0.81	0.82	
Stat. Significance	p-value			
Gr. B vs. Gr. A	0.61			
Gr. C vs Gr. A	0.73			
Gr. B vs Gr. C	0.39			
8-hour				
Mean	98.6	98.6	98.4	0.64
SD	0.65	1.04	0.86	
Stat. Significance	p-value			
Gr. B vs. Gr. A	0.36			
Gr. C vs Gr. A	0.46			
Gr. B vs Gr. C	-			

12-hour				
Mean	98.5	98.2	98.3	0.38
SD	0.59	0.87	1.02	
Stat. Significance	p-value			
Gr. B vs. Gr. A	0.31			
Gr. C vs Gr.A	0.77			
Gr. B vs Gr. C	0.13			

** statistically significant*

The mean distribution of cases by four-hourly grade of SpO2 was observed to be generally not statistically significant between Group B and Group C, and control Group

Table 6: Mean Distribution of cases by groups and RR

RR	Gr. B *(n=25)*	Gr. C *(n=25)*	Gr. A *(n=25)*	p-value
Pre-OP				
Mean	16.4	16.2	16.6	0.38
SD	1.04	0.91	1.08	
Stat. Significance	p-value			
Gr. B vs. Gr.A	0.43			
Gr. C vs Gr. A	0.16			
Gr. B vs Gr. C	0.57			
Intra operative				
Mean	16.4	16.6	17.5	0.002*
SD	0.92	1.19	1.26	
Stat. Significance	p-value			
Gr. B vs. Gr. A	0.001*			
Gr. C vs Gr. A	0.008*			
Gr. B vs Gr. C	0.69			
0-hour				
Mean	16.4	16.3	16.2	0.81
SD	0.91	0.79	0.91	
Stat. Significance	p-value			
Gr. B vs.Gr. A	0.54			
Gr. C vs Gr. A	0.74			
Gr. B vs Gr. C	0.74			
4-hour				
Mean	16.5	16.1	16.6	0.17
SD	0.96	0.83	1.04	
Stat. Significance	p-value			
Gr. B vs. Gr. A	0.78			
Gr. C vs Gr. A	0.08			
Gr. B vs Gr. C	0.12			
8-hour				
Mean	16.6	16.4	16.4	0.66
SD	0.92	0.86	0.91	

Stat. Significance Gr. B vs. Gr. A Gr. C vs Gr. A Gr. B vs Gr. C	p-value 0.15 0.62 0.35			
12-hour Mean SD	16.6 0.92	16.4 0.86	16.4 0.91	0.66
Stat. Significance Gr.B Ivs. Gr. A Gr. C vs Gr. A Gr. B vs Gr. C	p-value 0.44 - 0.43			

** statistically significant*

The mean distribution of cases by four-hourly grade of Respiratory Rate (RR) was observed to be generally not statistically significant between Group B and Group C,and control Group A

Table 7: Mean Distribution of cases by groups and HR

HR	Gr. B *(n=25)*	Gr. C *(n=25)*	Gr. A *(n=25)*	p-value
Pre-OP Mean SD	81.4 7.98	79.2 7.33	82.4 8.32	0.36
Stat. Significance Gr. B vs. Gr.A Gr.C vs Gr. A Gr. B vs Gr. C	p-value 0.67 0.16 0.32			
Intra oprative Mean SD	79.0 6.09	78.0 7.70	83.6 8.20	0.02*
Stat. Significance Gr. B vs. Gr.A Gr. C vs Gr. A Gr. B vs Gr. C	p-value 0.03* 0.02* 0.61			
0-hour Mean SD	79.7 7.67	77.4 6.65	81.6 8.21	0.15
Stat. Significance Gr. B vs. Gr. A Gr. C vs Gr. A Gr. B vs Gr. C	p-value 0.40 0.05* 0.26			
4-hour Mean SD	81.5 4.01	78.1 5.40	80.7 7.43	0.10
Stat. Significance Gr. B vs. Gr. A Gr. C vs Gr. A Gr. B vs Gr. C	p-value 0.62 0.16 0.02*			

8-hour				
Mean	81.1	81.5	81.7	0.95
SD	6.00	6.14	7.64	
Stat. Significance	p-value			
Gr. B vs. Gr. A	0.76			
Gr. C vs Gr. A	0.92			
Gr. B vs Gr. C	0.82			
12-hour				
Mean	80.4	83.5	81.3	0.18
SD	3.70	7.14	6.4	
Stat. Significance	p-value			
Gr. B vs. Gr. A	0.54			
Gr. C vs Gr. A	0.27			
Gr. B vs Gr. C	0.06			

** statistically significant*

The mean distribution of cases by four-hourly grade of Heart Rate (HR) was observed to be generally not statistically significant between Group B and Group C, and control Group A

Table 8: Mean Distribution of cases by groups and MAP

MAP	Gr. B *(n=25)*	Gr. C *(n=25)*	Gr. A *(n=25)*	p-value
Pre-OP				
Mean	79.5	80.7	82.6	0.03*
SD	3.38	4.79	3.89	
Stat. Significance	p-value			
Gr. B vs. Gr. A	0.004*			
Gr. C vs Gr. A	0.13			
Gr. Bvs Gr. C	0.31			
Intra operative				
Mean	81.0	80.2	80.1	0.82
SD	4.77	4.67	6.31	
Stat. Significance	p-value			
Gr. B vs. Gr. A	0.58			
Gr. C vs Gr. A	0.92			
Gr. B vs Gr. C	0.59			
0-hour				
Mean	81.3	81.6	81.5	0.97
SD	3.82	5.23	4.94	
Stat. Significance	p-value			
Gr. B vs.Gr. A	0.85			
Gr. C vs Gr. A	0.96			
Gr. B vs Gr. C	0.81			
4-hour				
Mean	79.2	79.4	81.7	0.09
SD	3.27	4.71	4.85	
Stat. Significance	p-value			
Gr. B vs. Gr. A	0.04*			
Gr. C vs Gr. A	0.10			
Gr. B vs Gr. C	0.84			

8-hour				
Mean	82.2	79.8	81.0	0.16
SD	3.57	5.90	3.61	
Stat. Significance	p-value			
Gr. B vs. Gr. A	0.21			
Gr. C vs Gr. A	0.39			
Gr. B vs Gr. C	0.08			
12-hour				
Mean	81.4	81.3	81.2	0.98
SD	3.29	5.47	4.58	
Stat. Significance	p-value			
Gr. B vs. Gr. A	0.83			
Gr. C vs Gr. A	0.96			
Gr. B vs Gr. C	0.90			

** statistically significant*

The mean distribution of cases by four-hourly MAP values was observed to be generally not statistically significant between Group B and Group C and control Group A

Table 9: Distribution of cases by groups and side effects

Co-morbid conditions	Gr. B		Gr. C		Gr. A		p-value
	No.	%	No.	%	No.	%	
AR							
Yes	1	4.0	0	0.0	0	0.0	0.36
No	24	96.0	25	100.0	25	100.0	
ND							
Yes	0	0.0	0	0.0	0	0.0	-
No	25	100.0	25	100.0	25	100.0	
PONV							
Yes	3	12.0	2	8.0	2	8.0	0.85
No	22	88.0	23	92.0	23	92.0	

$ not statistically significant

There seems to be no significant difference in the distribution of cases by Respiratory Depression, Post Operative Nausea and Vomiting and Neurological Deficit among the groups studied.

Table 10: Mean duration (in minutes) of effective analgesia of cases by groups

Duration of effective analgesia	Gr. B	Gr. A	Gr. A	p-value
No. of cases	25	25	25	
Mean	684.2	320.8	203.1	

S.D.	59.46	45.72	28.3	<0.001*
Median	645	320	200	
Mode	720	340	210	
Range	525-726	220-420	150-260	
Stat. Significance	p-value			
Gr. B vs. Gr. A	<0.001*			
Gr. C vs. Gr. A	<0.001*			
Gr. B vs. Gr. C	<0.001*			

** Statistically significant*

The mean duration of effective analgesia was significantly higher among Group B(684.2) than Group C (320.8; p<0.001) and control (203.1; p<0.001). The difference is statistically significant even when all three groups are compared together (p<0.001).

Table 11: Distribution of Mean duration of motor block by groups

Duration of motor block	Gr. B	Gr. C	Gr. A	p-value
No. of cases	25	25	25	
Mean	180.6	176.8	175.7	
S.D.	13.34	12.01	12.2	0.35
Median	180	180	180	
Mode	180	170	170	
Range	150-210	150-196	150-190	
Stat. Significance	p-value			
Gr. B vs. Gr. A	0.18			
Gr. C vs. Gr. A	0.74			
Gr. B vs. Gr. C	0.30			

$ not statistically significant

The mean distribution of cases by duration of motor block values was observed to be generally not statistically significant between Group B and Group C as well as between the groups and control.

DISCUSSION

The study of post-operative pain relief in patients undergoing various orthopaedic surgeries with 3.0ml of 0.5% [15mg] Bupivacaine [preservative free] +0.4 ml of 0.9% normal saline or 3.0ml of 0.5% Bupivacaine with 0.12mg (0.4 ml) Buprenorphine [preservative free] or 3.0ml of 0.5% Bupivacaine with 2mg [0.4ml] of midazolam [preservative free] given intrathecally.

In this study patient gets post-operative pain relief along with the intra-operative pain relief. The administration of suitable analgesics to the patients in pain is often inconvenient. Hence neuraxial additives is given along with bupivacaine as a single shot spinal anaesthesia

Sundnes et al[13] and bertil lofstrom[14] showed the time of onset of analgesia was between 2.mts -5mts.In our study the time of onset of analgesia was between 2.5-4mts in Groups A ,B and C. Our results correlates with studies done by Sundnes et al and Bertil Lofstrom.

The highest level of analgesia was T6 with 3.0ml of 0.5% hyperbaric Bupivacaine in study done by Stretting et al in 1982. In our study the highest level of analgesia was T6 in Group A, B and C. This result correlates with studies done by Stretting et al.[13]

Bertil Lofstrom[14] recommended 15mg of 0.5% hyperbaric Bupivacaine for lower extremity procedures and major hip surgery and the motor blockade[Grade III] duration was between 2.5-3hours.In our study the motor blockade[Grade III] of Group A; B and C patients was between 2.5-3.5hrs.This result correlates with studies done byBertil Lofstrom.

As per Jon Gjessing et al [1979] when the patient is treated prophylatically the amount of drug required is considerably less than that would be required if treatment was delayed until pain manifests and becomes intensified.In our study the amount of Buprenorphine required for

12hours of post-operative pain relief was 0.12mg and midazolam 2mg.

In our study all three groups of patients were comfortable during surgery except one patient in control group complained of pain but he did not require analgesia within two hours.From the second hour of post-operative period onwards,there was a significant change in the VAS reading-the control group patients showed more than 25mm in VAS scale [study group were still below 25mm of the pain scale.] Four patients required demand analgesia immediately after two hours.Ten patients demanded analgesia after three hours and ten patients required analgesia after four hours in control group.

In Group III only one patient demanded analgesia after three hours. Two patients started complaining of pain but demanded analgesia after four hours .Fifteen patients demanded analgesia after five hours, six patients demanded analgesia after six hours. One patient had effective analgesia upto seven hours.

In Group B all patients demanded analgesia only after 6 hrs and two patients did not demand analgesia upto twelve hours.Average time of demand for analgesia was between ten-twelve hours.In Group A Average time of demand for analgesia was between three –four hours and in Group C average time of demand analgesia was four –six hours.

Y.K Batra et al[15] and M.H.Kim et al[16] have used preservative free midazolam intrathecally with bupivacaine to increase the duration of postoperative analgesia in human beings.

Serrao et al[17] used the dose of 2 mg. of midazolam intrathecally to relieve chronic low backpain with good results.

In Group B post-operative pain relief with 0.12mg buprenorphine hydrochloride is upto

twelve hours

The duration of action of buprenorphine was 10 -15 hours according to studies by Cousins[18] and Glynn et al 1979.According to Sen Lipp.M[19]-upto thirteen hours analgesia with intrathecal 0.15mg buprenorphine achieved. Our study correlates with studies done by Sen Lipp.M

The ionger duration of action of buprenorphine is because of unusual receptor kinetics of the drug. Buprenorphine forms a very avid drug receptor complex, which tends to persist for longer duration without dissociation [Hambrook and Rance 1978]. The affinity of buprenorphine for opiate receptors is 50 times more than that of morphine.

The special receptor kinetics and high lipid solubility also explains buprenorphine`s longer duration of action compared to other lipid soluble drugs like Fentanyl which produces an intense sharply segmental and short lived analgesia due to rapid aggress for the cord [Bromage][20]

Nausea and vomiting is due to the rostral spread of opiod in spinal fluid to intracerebral structures including the vomiting center and chemoreceptor trigger zone.The locus of action is thought to be an vascularised area postrema lying specifically in the floor of IV ventricle

The incidence of post-operative nausea and vomiting ranged from none to 10% in studies done by Lanz et al,Chakraborthy 1984; Sen m 1992.[21,22]

Our results show that post-operative nausea and vomiting incidence in Group A is 4% and Group C is 8% and in Group C is 12%.Our results correlates with studies done by Lanz etal, Chakraborthy[1984] and Sen M [1992]

However the nausea and vomiting subsided without any treatment.The incidence of

nausea and vomiting is increased in post-operative ambulation.Since most of the patients in this study are in plaster of paris immobilization and cannot ambulate the incidence of nausea and vomiting were low.

The delayed respiratory depression is a known side effect of buprenorphine.Early respiratory depression, within one hour of injection seems to be due to vascular uptake and is transient[Bromage PR[3]] ,but the dangerous variety of delayed respiratory depression is intense and prolonged for many hours.

The respiratory depression is due to cephalad migration of opioid in CSF and subsequent reaction with opioid receptors located in ventral medulla.According to Harcus et al[23] the drug associated respiratory depression is estimated to be less than1%. According to Capogna et al[24] there was no respiratory depression in any of his cases receiving intrathecal bupivacaine with buprenorphine. In our study there was not a single case of respiratory depression in Groups A B and C. Our results correlates with studies done by Capogna et al.

Water soluble opioids like morphine produce respiratory depression more commonly than a lipophilic drug like buprenorphine.

Using sedation score of 0,1,2,3 the patients in Group A B and C were evaluated. In control group only 5 patients had mild sedation upto two hours. In midazolam group [Group C] 8 patients had a score of 2 and remaining 17 patients had sedation score of 1 upto one hour. Twenty patients had sedation score of 1 from two to four hours, only two patients found to be sedated from 4-6 hours in Group C.

In buprenorphine group,7 patients had sedation score of 2 and 10 patients had score of1 upto 4 hours.12 patients had sedation score of 2and 13 patients had sedation score of 1 from 4-8hours,19 patients had sedation score of 1 for 8-12hours and only four patient had sedation

score of one after 12hours.

In Group A and C there was no significant change in the self voiding time[urinary retention]. None of the patients complained of urinary retention and needed catheterization.

In Group B two patients had urinary retention and required catheterization [8%]. Gudy AR[25] [1987] reported urinary retention in 8% of his subjects. Chansoriya KP, Singh BP and Chauhan S[26] [Intrathecal Buprenorphine for post-operative pain relief 1987]reported urinary retention in 6% of their patients. Our results correlated with studies done by Gudy and Chansoriya et al 1987.No long term residual effects was noticed in any patients.

In Group B one patient complained of facial Pruritus. Facial Pruritus may be explained by the rapid penetration of the opioid to the superficially placed caudal portion of the nucleus of the spinal tract of trigeminal nerve. Also pruritus often subsides like loss of bladder function with subsequent doses of opioids presumably due to adaptation to the change in sensation. According to Cousins MJ and Mather allergic reaction is found minimally with opioid use[1984]. Our study correlates with Cousins MJ and Mather` s studies.[18]

In our study, the incidence of intra- operative complications like bradycardia and hypotension in all three groups are comparable and insignificant. According to Chansoriya[26] (1987) Lippin[19], 1987 there were no significant changes in pulse rate, BP and respiratory Rate, attributable to spinal Buprenorphine. There was no significant difference of requirement of crystalloids and dose of ephedrine hydrochloride. This results correlates with study done by Chansoriya (1987) Lippin, 1987.

In this study the drug buprenorphine is chosen because it is easily available and highly lipophilic hence diffusion of drug from CSF to neuraxis is faster and stay of drug in CSF is of less duration and there is less likelihood of rostral spread hence there was no respiratory

depression. It was decided to compare the post operative analgesia provided by buprenorphine with midazolam.

A number of experimental investigations were carried out to study the effects of intrathecal midazolam. It was found to produce reversible segmental antinociception without any evidence of neurotoxicity in both animals and human beings. (Goodchild et-al[27] & Serrao[17] & Murat Bahar[28])

Benzodiazepine receptors are present throughout the central nervous system including the spinal cord. (whitwam J.G.[29])

Goodchild C.S. demonstrated the administration of exogenous benzodiazepine3 in to the subarachnoid space. The drug reached to the benzodiazepine receptors – GABA A receptors in laminaII of dorsal horn of spinal cord[9].

In this study of post operative pain relief the route of administration of additives was by single shot subarachnoid injection. This procedure is commonly done in anaesthetic practice and easier when compared to epidural anaesthesia technique.

It has other advantages like rapid procedure, quick onset of analgesia, no need for fluid overloading and no appreciable changes in BP. PR and respiratory rate.

In this study none of the patient has exhibited any unwanted serious cardiovascular, respiratory and CNS effects which has proved buprenorphine and midazolam as safe & suitable agents for relief of post operative pain by intrathecal route. Because the duration of analgesia provided by buprenorphine is significantly greater than midazolam it can be a more suitable agent for post operative pain relief than midazolam especially when longer duration of post operative pain relief is warranted.

SUMMARY

A clinical study was undertaken to evaluate the efficacy, duration of pain relief and to know the quality of post-operative analgesia provided by neuraxial additives added to local anaesthetic agents.

The study was undertaken in 75 patients of ASA I and II posted for lower limb orthopaedic surgery for post operative pain relief Group-A. 25 patients received only 3.0ml of hyperbaric 15mg (3ml) preservative free bupivacaine +0.4ml of 0.9% normal saline intrathecally.

Group B - 25 patients 3.0ml of 0.5% hyperbaric bupivacaine (Preservative free) +0.12 mg(0.4ml) of buprenorphine (Preservative free) given intrathecally.

Group C - 25 patients - 3.0ml of 0.5% hyperbaric bupivacaine (Preservative free) + 2mg (0.4ml) of Midazolam (Preservative free) given intrathecally.

The onset time of analgesia in all three groups was 2½ - 4 minutes. The highest level of analgesia in all three group was upto T_6 level.

The motor blockade (Grade III) was upto three hours in these groups. The incidence of hypotension, bradycardia and pruitus were very low. The post-operative analgesia was upto 12 hours in Group B (S.D.59.46) and upto 6 hours in Group C (S.D.45.72).

None of the patients had any respiratory depression, but few patients had nausea and vomiting in the intra and post-operative period which was not severe. Urinary Retention (8%) and Pruritus (4%) was reported in a small percentage of patients in Group B.

Spinal buprenorphine is better than spinal midazolam in that it is useful for patients who require a longer period of pain relief in the Post-operative period and is not associated with significant Cardiovascular, Respiratory (or) Central Nervous system side effects.

Spinal opiate analgesia is better than parenteral opiates in that a smaller dose is sufficient, thereby reducing the side effects and the patients are not unduly sedated and the duration of analgesia is much longer than the parenteral route thereby avoiding repeated injections.

Spinal opiates score over spinal local anaesthetics in that there is no motor block which is unwanted in post-operative patients. The sympathetic block they produce may result in hypotension and importantly the duration of action of spinal opiates is much longer than spinal local anaesthetics.

The best drug amongst the spinal opiates is yet to be defined. Most of the studies have been done with morphine which is a hydrophilic drug and a liphophilic drug like buprenorphine has a definite edge as better concentration are achieved in the spinal cord and very little is left in CSF curtailing its rostral spread and depression of vital centers.

The optimal dose for an intrathecal administration is lesser than the doses for epidural route.

The addition of buprenorphine to the local anaesthetic agent bupivacine has not interfered with its action as for as duration of action, level of analgesia, the quality of the motor and sensory blockade (or) incidence of intra-operative complication like bradycardia, hypotension, nausea, vomiting etc. is considered.

A single intrathecal injection of buprenorphine with bupivacaine has produced not only

a satisfactory anaesthesia but also a prolonged post operative analgesia upto 12 hours, thereby avoiding the repeated im or IV injections and also improving the morale of the patient.

Buprenorphine 0.12mg (Preservative free) with heavy bupivacaine 15mg (0.5%) (Preservative free) is safe, cheap and provides good, and prolonged post operative analgesia without any significant side effects, compared to other available techniques. This correlates with the studies done by Sen Lipp M (1987).

CONCLUSION

Buprenorphine 0.12mg (0.4 ml preservative free) with hyperbaric 0.5% bupivacaine 15mg (preservative free) given by intrathecal route is safe, cheap and provides good and prolonged post-operative analgesia without any significant side effects when compared to midazolam 2 mg (0.4 ml preservative free) with hyperbaric 0.5% bupivacaine 15mg (preservative free) given by intrathecal route. So this combination can be used for providing prolonged post-operative analgesia for lower limb orthopaedic surgeries.

BIBLIOGRAPHY

1. Alfred Lee J., Atkinson R.S., Martret J., et al, Lumbar puncture and spinal analgesia (Intradural and Extradural) Churchill Livingstone, Edinburgh, 5th Edition.

2. Alfred Lee J., Atkinson R.S., Rushman G.B., et al, 'Synopsis of Anaesthesia" Butterworth, Heinemann Ltd., 1993, 11th Edn.

3. Philip R. Bromage, The price of intraspinal narcotic analgesia, "Anesthesia and Analgesia", 1981, 461. (Vol.60) No.7.

4. Aitkenhead A.R. and Smith G (1990). Text book of Anesthesia. Post – operative pain P.449 – 457.

5. Michael J Cousins, Medical Intelligence. Intrathecal and epidural administration of opioids, Anaesthesiology, 1984, 61, 276-310.

6. Cedric Prys Roberts, Andrew M.S. Black (1996). Management of postoperative pain. International practice of Anesthesia. P. 2/140/1-2/140/11.

7. Ray H.d. Amours. Michael Feerante (1997). Peri operative drugs and post – operative pain management. Anaesthesiology clinics of North America. 15 (2) : 251-260.

8. Robert K. Stoelting (1991) Midazolam. Pharmacology and Physiology in anaesthetic practice. P. 126 – 129.

9. Goodchild CS. GABA receptors and benzodiazepines. British Journal of Anesthesia 1993; 71:127-133.

10. Line. Peng YB., Willis W.D., (1996). Role of GABA receptor subtypes in inhibition of primate spinothalamic tract neurons. Journal of neurophysiology 75: 109-123.

11. Goodman and Gilman's pharmacological basis of therapeutics, 6th Edition, Hypnotics and Sedatives. P. 362 – 373.

12. Cowan, Lewis J.W., Agonist and antagonist properties of buprenorphine, A new anti-nociceptive agent, Brit. Journal Pharmacology (1977), 60, 537-545.

13. Sundnes K.O., Vaagenes P., Skretting P. et al, Spinal analgesia with hyperbaric bupivacaine, effects of volume of solution, Brit. Journal Anaesthesia, 1982, (54), 69.

14. Bertil Lofstrom J. and Mats Bengtsson, Spinal (intradural) and extradural analgesia, General Anaesthesia, 1987, (91) 1086 – 1092.

15. Batra Y.K. et.al. Addition of intrathecal Midazolam to Bupivacanie produces better post – operative analgesia without prolonging recovery – International Journal of Clinical pharmacology and Therapeutics – Vol 37 No.10/1999 519 – 523.

16. Kim K.M. and Lee Y.M. – Interthecal Midazolam increases the analgesic effects of spinal blockade with Buprevacaine in patients undergoing haemorrhoidecory – British Journal of Ananthesia – Jan 2001.

17. Serrao et.al(1992) – Intrathecal midazolam for the treatment of chronic mechanical low back pain – a controlled comparison with epidural steroid in a pilot study – pain 5.12.

18. Cousins J.M. and Mathur L.E., “Intrathecal and epidural administration of opioids”, Anesthesiology, 1984, 16, 276.

19. Lipp M., Lanz E., Daublander M., 0.15 mg of Intrathecal buprenorphine applied for post – operative analgesia. A double clinical blind study, Anesthesist, 1987, May 36 (5), 233-8.

20. Bromage P.R., Practice of spinal narcotic analgesia – Basic Consideration – Anesthesia and Analgesia, 1981, Vol. 60, 461.

21. Egon Lanz. Gabriele Simko, Dieter. T. et al. Extradural buprenorphine - A double blind study of post-operative analgesia and side effects. Anaesthesia - Analgesia (1984, 63, 593-8).

22. Sen. M., Intrathecal Buprenorphine for post-operative analgesia in orthopaedic surgery, J. Indian Med. Assoc., Jan 90 (1), 5-6.

23. Harcus A.H., Ward A.E., Smith D.W., Buprenorphine in post operative pain result in 7500 patients, Anesthesia 1980, Apr. 35 (4), 382-6.

24. Capogna G., Celleno D. Tagariello D. et al, Intrathecal buprenorphine for post operative analgesia in the elderly patients, Anesthesia 1988, Feb. 43 (2), 128-30.

25. Gudi A.R., Narcotic analgesic drug mixture of buprenorphine with xylocaine / bupivacaine by single shot extradural blockade and duration of post – operative pain relief, 1987, Vol.27, No.1.

26. Chansoriya K.P. Singh B.P., Chauhan S., Intrathecal buprenorphine for post – operative pain relief, Indian Journal Anaesthesia, 1987, 35 (5), 332.

27. Goodchild C.S. Guo Z. Musgreave A. and Gent J.P. (Dec. 1996) : Antinociception by Intrathecal Midazolam involves endogenous neurotransmitters acting at Spinal cord delta opioid receptors British Journal of Anesthesia 77: 758 – 76.3

28. Murat Bahar (1997). Spinal anesthesia with Midazolam in the rat. Canadian Journal of Anesthesia 44: 208-215.

29. Whitwam J.G. (1983) Benzodiazepine receptors (editorial). Anaesthesia, 38, 93-95.

30. Luke M., Kithata and Collins J.G., Spinal Action of Narcotic analgesics Anaesthesiology, (1981), 54, 153-163.

31. Alon E, Schulthess. G., Hossli G. et al, "A double blind comparison of Tramadol and buprenorphine in the control of post – operative pain", Anesthetist, 1981, 30 (12), 623-6.

32. Budd K, High dose of buprenorphine for post operative analgesia", Anesthesia, 1981 – 36 (9), 900 – 3.

33. Celleno d, Capogna G., Spinal buprenorphine for post – operative analgesia after caesarian section, Acta Anesthesiol Scand, 1989 Apr. 33 (3), 236-8.

34. Freedman M, A. comparison of buprenorphine and pentazocine for the relief of post – operative pain, South African Med. Journal 1986, Jan 4;69(1) 27-8.

35. Hovell. B.C. "Comprison of Buprenorphine, Pethidine and Pentazocine for the relief of pain after operation" British Journal Anaesthesia, 1977, 49; 913.

36. Mcquay H.J., Bullingham R., Paterson G.M., et al, Clinical effects of buprenorphine during and after operation, Brit. Journal Anaesthesia (1980), 52, 1013.

37. Obel D., Hansen L.K., Huttel M.S. et al, buprenorphine supplemented anaesthesia influence of dose and duration of analgesia, Brit. Journal of Anaesthesia (1985), 57, 271, 274.

38. Yonemura E, Influence of intrathecal morphine and buprenorphine on EEG and their analgesic effects, "Masui', 1990 Apr. 39(4), 478-86.

39. Veering B.T., Burm. A., "Spinal Anaesthesia with hyperbaric bupivacaine – Effects of age on neural blockade and pharmacokinetics", British Journal of Anaesthesia, 1988, 60, 187-194.

40. Valentice et. Al (1996) The effect of intrathecal midazolam on post – operative pain – European Journal of Anaesthesiology 1996. No; 13(6) 589-93.

41. Van Zundert AAJ, Grouls RJE, Korsten HHM, Lambert DH. Spinal anesthesia volume or concentration – what matters? Regional anaesthesia 1996; 21:112-8.

ANNEXURE

PROFORMA

POST-OPERATIVE ANALGESIA
A COMPARATIVE STUDY OF INTRATHECAL BUPIVACAINE WITH BUPRENORPHINE AND INTRATHECAL BUPIVACAINE WITH MIDAZOLAM

NAME :

HOSPITAL No. :

AGE :

SEX :

WEIGHT :

HEIGHT :

ASA STATUS :

DIAGNOSIS :

SURGERY :

DURATION :

PRE-OPERATIVE :

CVS	MAP	RR	
RS	PULSE	SpO_2	

DOSE :
1. Bupivacaine (0.5%) Heavy 3.0 CC (15 mgs.)
2. Buprenorphine (Preservative Free) 0.4 ml (0.12 mg)
3. Midazolam (Preservative Free) 0.4 ml (2 mg)

POST-OPERATIVE EVALUATION

Variables	Peak Intra Op	POST OPERATIVE PERIOD (MINUTES)												
		0	30	60	90	120	150	180	210	240	270	300	330	360
Sensory Level														
Heart Rate														
MAP														
Respiratory Rate														
SpO_2														
VAS														
Recovery from Motor Block														
First Demand Analgesia														
Time of First Self-voiding														
SIDE EFFECTS														
Nausea														
Vomiting														
Sedation														
Allergic Reactions														
Neurological Defecit														